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DOCUMENT-IDENTIFIER: US 6248516 B1  
TITLE: Single domain ligands, receptors comprising said ligands  
methods for their  
production, and use of said ligands and receptors  
DATE-ISSUED: June 19, 2001  
INVENTOR-INFORMATION:  
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US-CL-CURRENT: 435/6,435/252.33 ,435/441 ,435/446 ,435/69.6

CLAIMS:

What is claimed is:

1. A library for expression of immunoglobulin heavy chain variable domains (VH domains), said library comprising a repertoire of nucleic acid sequences encoding a third CDR of an immunoglobulin heavy chain variable domain, each member of said repertoire being flanked by VH sequences so as to provide nucleic acid encoding a repertoire of immunoglobulin heavy chain variable domains which are identical except for said third CDR.
2. A library according to claim 1 wherein said third CDRs are derived from preexisting repertoires of CDRs.
3. A library according to claim 1 wherein said third CDRs comprise random sequences.
4. A library according to claim 1 wherein said nucleic acid encoding a repertoire of immunoglobulin heavy chain variable domains further comprises a sequence encoding one or more constant domains for expression of Ig-type chains.
5. A method for generating an antibody variable domain expression library having a diversity of CDR3 sequences, said method comprising: providing expression vectors, said vectors comprising a variable domain encoding sequence of an antibody; introducing by mutagenesis a diversity of CDR3 sequences into

said variable domain  
encoding sequence; and  
recovering an expression library having a diversity of binding  
activities.

6. The method of claim 5 wherein said antibody variable domain  
is a VH domain.

7. The method of claim 5 wherein said expression vector encodes  
an Fab antibody  
fragment.

8. The method of claim 5 wherein said expression vector encodes  
a scFv fragment.

9. An expression library which expresses antibody variable  
domains, said library  
comprising a universal set of framework regions carrying a  
diversity of CDR3  
sequences, said library having a diversity of binding activities.

10. The expression library of claim 9 wherein said antibody  
variable domains are VH  
domains.

11. The expression library of claim 9 wherein said antibody  
variable domains are VL  
domains.

12. The expression library of claim 9 wherein said variable  
domains are expressed  
in the form of Fab antibody fragments.

13. An expression library which expresses antibody variable  
domains having CDR  
diversity in only the CDR3 sequences, said library having a  
diversity of binding  
activities.

14. The expression library of claim 13 wherein said antibody  
variable domains are  
VH domains.

15. The expression library of claim 13 wherein said antibody  
variable domains are  
VL domains.

16. The expression library of claim 13 wherein said variable  
domains are expressed  
in the form of Fab antibody fragments.

17. The expression library of claim 13 wherein said variable  
domains are expressed  
in the form of scFv antibody fragments.

18. An expression library produced by the method of claim 5.

19. An expression library produced by the method of claim 6.

20. An expression library produced by the method of claim 7.

21. An expression library produced by the method of claim 8.

US-PAT-NO: 6225447

DOCUMENT-IDENTIFIER: US 6225447 B1

TITLE: Methods for producing members of specific binding pairs

DATE-ISSUED: May 1, 2001

INVENTOR-INFORMATION:

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US-CL-CURRENT: 530/387.3

CLAIMS:

What is claimed is:

1. A specific binding pair member which is a single chain specific binding pair member comprising a first polypeptide chain component and a second polypeptide chain component and specific for a complementary specific binding pair member of interest, produced by a method which comprises:

- (I) introducing into host cells;
- (i) first vectors comprising nucleic acid encoding a genetically diverse population of a first polypeptide chain component fused to a component of a secreted replicable genetic display package for display of said polypeptide chain component at the surface of replicable genetic display packages; and
- (ii) second vectors comprising nucleic acid encoding a genetically diverse population of said second polypeptide chain component; said first vectors being packaged in infectious replicable genetic display packages and their introduction into host cells being by infection into host cells harboring said second vectors; or
- said second vectors being packaged in infectious replicable genetic display packages and their introducing into host cells being by infection into host cells harboring said first vectors;

(II) causing or allowing recombination between said first and second vectors within said host cells, the recombination being promoted by inclusion in said first and second vectors of sequences at which site-specific recombination occurs resulting in recombinant vectors each of which comprises nucleic acid encoding a said single chain specific binding pair member comprising a said first polypeptide chain component and a said second polypeptide chain component and an amino acid sequence encoded by a sequence provided by recombination between said sequences at which site-specific recombination occurs, and capable of being packaged into a replicable genetic display packages using said replicable genetic display package component;

(III) expressing said single chain specific binding pair members within the host cells to form a library of said single chain specific binding pair members displayed by replicable genetic display packages, whereby the genetic materials of each said replicable genetic display package encodes a single chain specific binding pair member displayed at its surface,

(IV) selecting by binding with said complementary specific binding pair member of interest one or more single chain specific binding pair members specific for said complementary specific binding pair member of interest, each single chain specific binding pair member thus selected being associated in its respective replicable genetic display package with nucleic acid encoding that single chain specific binding pair member,

(V) obtaining nucleic acid encoding a said single chain specific binding pair member from its replicable genetic display package displaying a single chain specific binding pair member selected in step (IV);

(V) producing, by expression of encoding nucleic acid in a recombinant host organism, a single chain specific binding pair member comprising a first polypeptide chain component and a second polypeptide chain component and an amino acid sequence encoded by a sequence provided by recombination between said sequences at which

site-specific recombination occurs and specific for said  
 complementary specific  
 binding pair member of interest, which single chain specific  
 binding pair comprises  
 a polypeptide chain component which is as encoded by nucleic acid  
 encoding a said  
 polypeptide chain component of a specific binding pair member  
 selected in step (IV)  
 or is a derivative thereof by way of addition, deletion,  
 substitution or insertion  
 of one or more amino acids or by linkage of another molecule.

2. A specific binding pair member according to claim 1 wherein  
 at least one of said  
 first and second vectors is a phage vector.

3. A specific binding pair member according to claim 1 wherein  
 expression in said  
 step (III) is from a phagemid vector, the method including using  
 a helper phage or a  
 plasmid expressing complementing phage genes, to help package  
 said phagemid genome,  
 and said component of the replicable genetic display package is a  
 capsid protein  
 therefor.

4. A specific binding pair member according to claim 1 wherein  
 either or both of  
 the populations of said first and second polypeptide chain  
 components is derived  
 from a repertoire selected from the group consisting of:
 

- (i) the repertoire of rearranged immunoglobulin genes of an  
 animal immunized with a  
 complementary sbp member;
- (ii) the repertoire of rearranged immunoglobulin genes of an  
 animal not immunized  
 with a complementary sbp member;
- (iii) a repertoire of an artificially rearranged immunoglobulin  
 gene or genes;
- (iv) a repertoire of an immunoglobulin homolog gene or genes;
- (v) a repertoire of sequences derived from a germ-line  
 immunoglobulin gene or genes;
- (vi) a repertoire of an immunoglobulin gene or genes artificially  
 mutated by the  
 introduction of one or more point mutations; and
- (vii) a mixture of any of (i), (ii), (iii), (iv), (v) and (vi).

5. A specific binding pair member according to claim 1 wherein  
 the replicable  
 genetic display package is a bacteriophage, the host is a  
 bacterium, and said  
 component of the replicable genetic display package is a capsid  
 protein for the  
 bacteriophage.

6. A specific binding pair member according to claim 5 wherein

the phage is a  
filamentous phage.

7. A specific binding pair member according to claim 6 wherein  
the phage is  
selected from the class I phages fd, M13, Ifl, Ike, ZJ/Z, Ff and  
the class II phages  
Xf, Pfl and Pf3.

8. A specific binding pair member according to claim 6 wherein  
the first  
polypeptide chain components are expressed as fusions with the  
gene III capsid  
protein of phage fd or its counterpart in another filamentous  
phage.

9. A specific binding pair member according to claim 8 wherein  
the first  
polypeptide chain components are each inserted in the N-terminal  
region of the  
mature capsid protein downstream of a secretory leader peptide.

10. A specific binding pair member according to claim 5 wherein  
the first  
polypeptide chain components are expressed as fusions with the  
gene III capsid  
protein of phage fd or its counterpart in another filamentous  
phage.

11. A specific binding pair member according to claim 10 wherein  
the first  
polypeptide chain components are each inserted in the N-terminal  
region of the  
mature capsid protein downstream of a secretory leader peptide.

12. A specific binding pair member according to claim 5 wherein  
the host is E.  
coli.

13. A specific binding pair member according to claim 1, wherein  
said sequences at  
which site-specific recombination occurs are loxP sequences.

14. A specific binding pair (sbp) member which is a single chain  
specific binding  
pair member specific for a counterpart specific binding pair  
member of interest,  
produced by a method which comprises:

(i) causing or allowing intracellular recombination between (a)  
first vectors  
comprising nucleic acid encoding a population of a fusion of a  
first polypeptide  
chain component of a specific binding pair member and a component  
of a secreted  
replicable genetic display package and (b) second vectors  
comprising nucleic acid  
encoding a population of a second polypeptide chain component of  
a specific binding  
pair member, at least one of said populations being genetically

diverse, the recombination between the vectors being at sequences at which site-specific recombination occurs and resulting in recombinant vectors each of which comprises nucleic acid encoding a single chain specific binding pair member comprising a said first polypeptide chain component, a said second polypeptide chain component, and an amino acid sequence encoded by a sequence provided by recombination between said sequences at which site-specific recombination occurs, which nucleic acid is capable of being packaged using said replicable genetic display package component; and

(ii) expressing said single chain specific binding pair members producing replicable genetic display packages which display at their surface said single chain specific binding pair members and which each comprise nucleic acid encoding a said single chain specific binding pair member

(iii) selecting by binding with said counterpart specific binding pair member of interest one or more single chain specific binding pair members specific for said counterpart specific binding pair member of interest, each single chain specific binding pair member thus selected being associated in its respective replicable genetic display package with nucleic acid encoding that single chain specific binding pair member;

(iv) obtaining nucleic acid encoding a said single chain specific binding pair member from its replicable genetic display package displaying a specific binding pair member selected in step (v);

(v) producing, by expression of encoding nucleic acid in a recombinant host organism, a said single chain specific binding pair member comprising a first polypeptide chain component and a second polypeptide chain component and an amino acid sequence encoded by a sequence provided by recombination between said sequences at which site specific recombination occurs and specific for said complementary specific binding pair member of interest, which single chain specific binding pair member comprises a polypeptide chain component which is as encoded by

nucleic acid encoding  
a said polypeptide chain component of a specific binding pair  
member selected in  
step (v) or is a derivative thereof by way of addition, deletion,  
substitution or  
insertion of one or more amino acids or by linkage of another  
molecule.

15. A specific binding pair member according to claim 14 wherein  
the sequences at  
which site-specific recombination occurs are loxP sequences and  
site-specific  
recombination is catalysed by Cre-recombinase.

16. A specific binding pair member according to claim 14 wherein  
the first vectors  
are phages or phagemids and the second vectors are plasmids, or  
the first vectors  
are plasmids and the second vectors are phages or phagemids, and  
the intracellular  
recombination takes place in a bacterial host which replicates  
plasmids  
preferentially over phages or phagemids, or which replicates  
phages or phagemids  
preferentially over plasmids.

17. A specific binding pair member according to claim 16 wherein  
said bacterial  
host is a PolA strain of E. coli or of another gram-negative  
bacterium.

18. A specific binding pair member according to claim 17 which  
comprises an  
antibody antigen-binding domain.

19. A specific binding pair member according to claim 14 which  
comprises a single  
chain Fv immunoglobulin molecule.

US-PAT-NO: 6172197

DOCUMENT-IDENTIFIER: US 6172197 B1

TITLE: Methods for producing members of specific binding pairs

DATE-ISSUED: January 9, 2001

INVENTOR-INFORMATION:

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, 530/412 , 530/867 , 536/23.1 , 536/23.4 , 536/23.53

CLAIMS:

What is claimed is:

1. A library of filamentous bacteriophage particles displaying on their surface as a fusion with a gene III coat protein surface component a genetically diverse population of specific binding pair members in functional form comprising a binding domain for complementary binding specific binding pair members, said specific

binding pair members encoded by nucleic acid derived from a natural repertoire of nucleic acids encoding said genetically diverse population of specific binding pair members, the particles each containing a phagemid genome which is plasmid nucleic acid containing a single stranded phage replication origin and a nucleotide sequence encoding said fusion, and the particle having a coat partially derived from a helper phage and partly from said fusion.

2. A library according to claim 1 wherein the specific binding pair members comprise a binding domain of an immunoglobulin.

3. A library according to claim 2 wherein the specific binding pair members are scFv molecules.

4. A library according to claim 2 wherein the specific binding pair members comprise Fab molecules.

5. The library of claims 2, 3, or 4 wherein the natural repertoire of specific binding pair members is encoded by nucleic acid derived from an animal unimmunized against the complementary specific binding pair member.

6. The library of claims 2, 3, or 4 wherein the natural repertoire of specific binding pair members is encoded by nucleic acid derived from an animal immunized against the complementary specific binding pair member.

US-PAT-NO: 6140471

DOCUMENT-IDENTIFIER: US 6140471 A

TITLE: Methods for producing members of specific binding pairs

DATE-ISSUED: October 31, 2000

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US-CL-CURRENT: 530/387.3

CLAIMS:

What is claimed is:

1. A specific binding pair member which is a single chain specific binding pair member comprising a first polypeptide chain component and a second polypeptide chain component and which is specific for a complementary specific binding pair member of interest, produced by a method having the following steps:

- (a) introducing into prokaryotic host cells
  - (i) first vectors comprising nucleic acid encoding a genetically diverse population of said first polypeptide chain component fused to a component of a secreted replicable genetic display package for display of said polypeptide chain components at the surface of replicable genetic display packages; and
  - (ii) second vectors comprising nucleic acid encoding a genetically diverse population of said second polypeptide chain components; said first vectors being packaged in infectious replicable genetic display packages and their introduction into prokaryotic host cells being by infection into prokaryotic host cells harbouring said second vectors, or said second vectors being packaged in infectious replicable genetic display packages

and their introduction into prokaryotic host cells being by infection into host cells harbouring said first vectors; and

(b) causing or allowing recombination between said first and second vectors within said prokaryotic host cells, the recombination being promoted by inclusion in said first and second vectors of sequences at which site-specific recombination occurs, which sequences at which site-specific recombination occurs are derived from a loxP sequence, resulting in recombinant vectors each of which comprises nucleic acid encoding a said single chain specific binding pair member comprising a said first polypeptide chain component and a said second polypeptide chain component and an amino acid sequence encoded by a sequence provided by recombination between said sequences at which site-specific recombination occurs, and capable of being packaged into a replicable genetic display packages using said replicable genetic display package component;

(c) expressing said single chain specific binding pair members, producing replicable genetic display packages which display at their surface said single chain specific binding pair members and which each comprise nucleic acid encoding a said single chain specific binding pair member;

(d) selecting by binding with said complementary specific binding pair member of interest one or more single chain specific binding pair members specific for said complementary specific binding pair member of interest, each single chain specific binding pair member thus selected being associated in its respective replicable genetic display package with nucleic acid encoding that single chain specific binding pair member;

(e) obtaining nucleic acid encoding a single chain specific binding pair member from its replicable genetic display package displaying a specific binding pair member selected in step (d);

(f) producing, by expression of encoding nucleic acid in a recombinant host organism, a single chain specific binding pair member comprising a first polypeptide

chain component and a second polypeptide chain component and an amino acid sequence encoded by a sequence provided by recombination between said sequences at which site-specific recombination occurs and specific for said complementary specific binding pair member of interest, which single chain specific binding pair comprises a first polypeptide chain component which is as encoded by nucleic acid encoding a said first polypeptide chain component of a specific binding pair member selected in step (d) or is a derivative thereof by way of addition, deletion, substitution or insertion of one or more amino acids or by linkage of another molecule, and a second polypeptide chain component which is as encoded by nucleic acid encoding a said second polypeptide chain component of a specific binding pair member selected in step (d) or is a derivative thereof by way of addition, deletion, substitution or insertion of one or more amino acids or by linkage of another molecule.

2. A specific binding pair member according to claim 1 comprising an antibody antigen binding domain.

3. A specific binding pair member according to claim 2 which comprises a single chain Fv molecule.

4. A specific binding pair member according to claim 1 wherein said replicable genetic display packages are secreted bacteriophage.

5. A specific binding pair member according to claim 2 wherein said replicable genetic display packages are secreted bacteriophage.

6. A specific binding pair member according to claim 3 wherein said replicable genetic display packages are secreted bacteriophage.

7. A specific binding pair member according to claim 1 wherein the recombination takes place in a bacterial host which replicates phages or phagemids preferentially over plasmids.

8. A specific binding pair member according to claim 7 wherein said bacterial host is a PolA strain of E. coli or of another gram-negative bacterium.

9. A specific binding pair member according to claim 2 wherein the recombination takes place in a bacterial host which replicates phages or

phagemids preferentially  
over plasmids.

10. A specific binding pair member according to claim 9 wherein  
said bacterial host  
is a PolA strain of E. coli or of another gram-negative  
bacterium.

11. A specific binding pair member according to claim 3 wherein  
the recombination  
takes place in a bacterial host which replicates phages or  
phagemids preferentially  
over plasmids.

12. A specific binding pair member according to claim 11 wherein  
said bacterial  
host is a PolA strain of E. coli or of another gram-negative  
bacterium.

13. A specific binding pair member according to claim 4 wherein  
the recombination  
takes place in a bacterial host which replicates phages or  
phagemids preferentially  
over plasmids.

14. A specific binding pair member according to claim 13 wherein  
said bacterial  
host is a PolA strain of E. coli or of another gram-negative  
bacterium.

15. A specific binding pair member according to claim 5 wherein  
the recombination  
takes place in a bacterial host which replicates phages or  
phagemids preferentially  
over plasmids.

16. A specific binding pair member according to claim 15 wherein  
said bacterial  
host is a PolA strain of E. coli or of another gram-negative  
bacterium.

17. A specific binding pair member according to claim 6 wherein  
the recombination  
takes place in a bacterial host which replicates phages or  
phagemids preferentially  
over plasmids.

18. A specific binding pair member according to claim 17 wherein  
said bacterial  
host is a PolA strain of E. coli or of another gram-negative  
bacterium.

US-PAT-NO: 6017732

DOCUMENT-IDENTIFIER: US 6017732 A

TITLE: Bacteriophage library displaying immunoglobulin  
repertoires with a chemical  
moiety covalently bound within the binding site: production and  
selection thereof

DATE-ISSUED: January 25, 2000

INVENTOR-INFORMATION:

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, 435/71.1 , 530/350  
, 530/387.1 , 530/387.3 , 530/402

CLAIMS:

We claim:

1. A diverse repertoire of first specific binding pair (sbp).  
members each having a  
binding site for second sbp member and each being fused to a  
surface component of a  
bacteriophage, wherein each first sbp member has a first  
polypeptide domain which  
comprises a binding region of immunoglobulin heavy chain variable  
domain (VH) and a  
second polypeptide domain which comprises a binding region of an  
immunoglobulin  
light chain variable domain (VL), the first and in that each  
binding site comprises  
a chemical moiety bound covalently at an amino acid residue  
within the binding site.
2. A method of providing a diverse repertoire of first specific  
binding pair (sbp)  
members each of which has a binding site and is fused to a  
surface component of a  
bacteriophage, each first sbp member having a first polypeptide  
domain which  
comprises a binding region of an immunoglobulin heavy chain  
variable domain (VH) and  
a second polypeptide domain which comprises a binding of an

immunoglobulin light chain variable domain (VL), the first and second polypeptide domains forming the binding site, the method being characterized by a step of chemical modification of first sbp members in the repertoire to introduce a chemical moiety bound covalently to an amino acid residue in the binding site of each first sbp member.

3. A method according to claim 2 wherein provision of the repertoire of first sbp members before the step of chemical modification comprises expression from a population of nucleic acid molecules collectively encoding the repertoire.

4. A method according to claim 3 wherein provision of the population of nucleic acid molecules comprises a step of mutation of nucleic acid encoding first sbp member, or a polypeptide component part thereof, to introduce a codon encoding the amino acid residue.

5. A method according to claim 2 wherein the amino acid residue is selectively modified in each first sbp member.

6. A method according to claim 2 wherein the population of nucleic acid molecules is provided by joining gene fragments.

7. A method according to claim 2 wherein the chemical modification is performed in vitro.

8. A method according to claim 2 comprising, following said chemical modification, a step of selection of a first sbp member with a binding site able to bind a second sbp member of interest.

9. A method according to claim 8 wherein the selection is by binding with second sbp member of interest.

10. A method according to claim 8 wherein binding of the selected first sbp member to the second sbp member of interest is enhanced compared with binding of that first sbp member without said chemical moiety.

11. A method according to claim 8 wherein binding of the selected first sbp member to the second sbp member of interest is dependent on the presence of the chemical moiety bound covalently at said amino acid.

12. A method according to claim 8 wherein the first sbp members are expressed fused

to a surface component of a bacteriophage so that each bacteriophage in a population thereof thereby displays a first sbp member at its surface, each bacteriophage in the population containing a nucleic acid molecule which encodes the first sbp member displayed at its surface.

13. A method according to claim 12 wherein selection of a first sbp member with a binding site able to bind a second sbp member of interest is followed by recovery of a sequence of nucleotides from the bacteriophage which displays the selected first sbp member on its surface.

14. A method according to claim 13 wherein the sequence of nucleotides is used in the production of a first sbp member with a binding site able to bind that second sbp member of interest.

15. A method of providing a genetically diverse repertoire of first specific binding pair (sbp) members each of which has a binding site for complementary second sbp member and is fused to a surface component of a bacteriophage, each first sbp member having a first polypeptide domain which comprises a binding region of an immunoglobulin heavy chain variable domain (VH) and a second polypeptide domain which comprises a binding region of an immunoglobulin light chain variable domain (VL) the first and second polypeptide domains forming the binding site, the method comprising:

provision of a population of nucleic acid molecules collectively encoding a genetically diverse repertoire of first sbp members, the binding site of the encoded first sbp members each having an amino acid residue which is selectively modifiable to introduce a covalently bound chemical moiety into the binding site; expression from the nucleic acid to provide a repertoire of first sbp members.

16. A method according to claim 15 wherein provision of the population of nucleic acid molecules comprises a step of mutation of nucleic acid encoding first sbp member, or a polypeptide component part thereof, to introduce a codon encoding the amino acid residue.

17. A method according to claim 15 wherein the population of nucleic acid molecules is provided by joining gene fragments.

18. A method according to claim 15 comprising chemical modification of first sbp members in the repertoire thereof at said amino acid residue to introduce a covalently bound chemical moiety into the binding site.

19. A method according to claim 18 comprising, following said chemical modification, a step of selection of first sbp member with a binding site able to bind a second sbp member of interest.

20. A method according to claim 19 wherein the selection is by binding with second sbp member of interest.

21. A method according to claim 19 wherein binding of the selected first sbp member to the second sbp member of interest is enhanced compared with binding of that first sbp member without said chemical moiety.

22. A method according to claim 19 wherein binding of the selected first sbp member to the second sbp member of interest is dependent on the presence of the chemical moiety bound covalently at the amino acid.

23. A method according to claim 19 wherein the first sbp members are expressed fused to a surface component of a bacteriophage so that each bacteriophage in a population thereof thereby displays a first sbp member at its surface, each bacteriophage in the population containing a nucleic acid molecule which encodes the first sbp member displayed at its surface.

24. A method according to claim 23 wherein selection of a first sbp member with a binding site able to bind a second sbp member of interest is followed by recovery of a sequence of nucleotides from the bacteriophage which displays the selected first sbp member on its surface.

25. A method according to claim 24 wherein the sequence of nucleotides is used in the production of a first sbp member with a binding site able to bind that second sbp member of interest.